March 5, 1999

Bruce Nye, Esquire
Adams, Nye, Sinunu and Walker, LLP
One Jackson Place
633 Battery Street, 5th Floor
San Francisco, California 94111

Michael S. Marcus, Esquire
Akin, Gump, Strauss, Hauer and Feld, LLP
1333 New Hampshire Avenue, NW, Suite 400
Washington, DC 20036

Dear Mr. Marcus and Mr. Nye:

Thank you for your recent petition on behalf of Baxter Healthcare Corporation entitled "Petition for Determination that Exposure to Di(2-ethylhexyl)phthalate ("DEHP") from Prescription Medical Devices Does Not Pose a Significant Risk of Cancer to Humans, Determination that Proposition 65 Warnings Are Not Required for Prescription Medical Devices, and Other Requested Relief." Briefly, the petition asks the Office of Environmental Health Hazard Assessment (OEHHA) to take seven regulatory actions and two procedural actions concerning DEHP and/or medical devices as they relate to Proposition 65. Listed below is each of the requested actions (paraphrased) along with OEHHA's response:

Requested Regulatory Actions:

(a) Determine and promulgate regulations stating that there is lack of substantial or sufficient evidence to conclude that DEHP poses a significant risk of cancer to humans by the non-oral or oral route of exposure and therefore no Proposition 65 warning is required for exposure to DEHP.

In order for such a determination to be made, OEHHA would need to find that the available data indicate that exposure to DEHP by any route poses no additional cancer risk to humans. OEHHA acknowledges that a substantial body of scientific literature concerning DEHP and the class of compounds known as peroxisome proliferators has developed in recent years, particularly with respect to the role the peroxisome proliferator-activated receptors (PPARs) and cell proliferation may play in the carcinogenic process. At this point, however, OEHHA does not find this new body of

evidence points toward a determination that human exposure to any level of DEHP is without carcinogenic risk. Rather, the literature presents data that leave open the possibility of human sensitivity to DEHP's carcinogenic effects. This includes evidence for a multiplicity of effects mediated by PPARs, evidence that humans have and express relevant PPAR genes, and evidence that cellular events mediated by PPARs separate from peroxisome proliferation and oxidative DNA damage may be operative in the carcinogenic response to DEHP. Thus, based on the available scientific evidence, OEHHA is not willing to take the requested regulatory action. OEHHA has actively followed the scientific developments regarding the carcinogenicity of DEHP and has produced a recent evaluation which considered much of the body of evidence which has become available since the Proposition 65 listing in 1988 (Public Health Goals for Drinking Water, 1998 (enclosed)). In its evaluation of MTBE for development of a public health goal, OEHHA continues to recognize the potential carcinogenic risk of DEHP to humans by the oral route and discusses the current uncertainty regarding DEHP's possible carcinogenic mode(s) of action. The petition does not appear to contain substantial new evidence not already considered by OEHHA on these issues.

In addition, OEHHA has followed the scientific literature with regard to DEHP's potential to cause cancer by the non-oral route. Some of the recent information has also been submitted as part of this petition. The convention in carcinogen risk assessment is to assume that a carcinogen by one route of exposure will be carcinogenic by other routes in the absence of credible evidence to the contrary. The petition's argument for the safety of non-oral routes of exposure relies on the following assertions: DEHP's carcinogenic effects on the liver of rodents are mediated by its primary metabolite, mono(2-ethylhexyl)phthalate (MEHP); MEHP is generated in the gut by pancreatic lipases and non-oral routes of exposure bypass the gut and thus also the formation of MEHP. Accepting the premise of DEHP's safety by non-oral routes requires accepting these assertions. A survey of the available literature reveals human evidence contrary to this hypothesis. This includes evidence for the formation of MEHP (by human plasma esterases) in polyvinyl chloride blood packs, formation of MEHP in the plasma of newborn infants subjected to exchange transfusions (*in vivo* and *ex vivo* generation), formation of MEHP perioperatively in patients undergoing a variety of surgical procedures from heart transplants in adults to corrections of congenital defects in infants, and formation of MEHP in patients undergoing hemodialysis. It appears, therefore, that (1) metabolism of DEHP occurs at sites other than the gut and (2) significant MEHP appears in the blood of individuals exposed to DEHP by non-oral routes. Given that OEHHA finds that DEHP poses a carcinogenic risk by the oral route, this evidence alone presents a barrier to a conclusion that non-oral routes of exposure to DEHP do not also pose some carcinogenic risk. Thus, OEHHA will not take the requested action regarding the non-oral route of exposure.

(b) Promulgate an exemption from the Proposition 65 cancer warning requirement for DEHP-containing prescription medical devices where human exposure to DEHP is limited to non-oral exposure.

This request is essentially a "subset" of the request set forth above in item (a). That is, assuming OEHHA had granted the relief sought in item (a), it would then make some sense to promulgate the regulation requested in this item. However, OEHHA is not at this time granting the relief sought by item (a). Since DEHP will, therefore, stay on the Proposition 65 list in an unmodified fashion, OEHHA cannot and does not grant the regulatory action sought in this item. That is, there is no basis for promulgating a regulation to exempt DEHP-containing prescription medical devices from the Proposition 65 warning requirements for exposure to DEHP via the non-oral exposure pathway, since DEHP remains on the Proposition 65 list for all routes of exposure.

(c) Make a determination that DEHP presents no significant cancer risk by non-oral routes of exposure.

As mentioned above (see response to item (a)), OEHHA does not find the available evidence sufficient to conclude that all non-oral routes of exposure to DEHP are without potential carcinogenic risk to humans. Thus, OEHHA is not prepared to make this determination.

(d) Revise the listing of DEHP to restrict the cancer listing to “DEHP by oral route of exposure.”

DEHP was added to the Proposition 65 list of chemicals known to the state to cause cancer by the “state’s qualified experts” mechanism without restriction as to route of exposure. OEHHA does not have the authority to modify this listing. Only the Carcinogen Identification Committee (CIC) of the Science Advisory Board (SAB) has the authority to modify a listing for a chemical it, or a predecessor entity, placed on the list. For the initiation of such a process, the petitioner is referred to a mechanism for reconsideration of agents on the Proposition 65 list presented in an OEHHA document entitled “Mechanisms for Removing Chemicals from the Proposition 65 List Based on Findings Made by the ‘State’s Qualified Experts’.” This document is available at http://www.oehha.ca.gov/prop65/policy docs.html.

(e) Determine that requiring a manufacturer of FDA-prescription medical devices to provide a Proposition 65 warning directly to patients is in violation of the law of informed consent.

The petition seeks to have OEHHA adopt a regulation stating the provisions of Proposition 65 as they relate to medical devices are "in violation of the law of informed consent and other laws of the State of California . . . and that no manufacturer of a FDA – regulation (sic) prescription medical device is required to provide directly to patients a Proposition 65 warning under [Health and Safety Code] Section 25249.6 or any other section or regulation of Proposition 65 [the Safe Drinking Water and Toxic Enforcement Act of 1986]."

OEHHA has reviewed this request and determined that it does not have the authority to grant the relief requested. More specifically, although OEHHA is the lead agency for implementation of Proposition 65, it does not have the authority to list, modify listings, or remove chemicals from the Proposition 65 list of its own volition. (OEHHA does have authority to place chemicals on the list via the administrative listing mechanisms.) Rather, the State's qualified experts, the SAB composed of the CIC and the Developmental and Reproductive Toxicant Identification Committee, have the authority to decide to list, modify listings, or delist chemicals under Proposition 65. (Health and Safety Code §25249.8(b)).

In addition to the above reason, pursuant to the California Constitution, Article III, Section 3.5, OEHHA lacks the authority to declare Proposition 65 to be in conflict with other laws, to refuse to enforce Proposition 65 as drafted based on the contention that it is in conflict with other laws, or otherwise refuse to enforce Proposition 65 unless and until "an appellate court has made a determination that such statute is unconstitutional." (Cal. Const. Art. III, Sec. 3.5)

Section 3.5 reads in its entirety as follows:

> An administrative agency, including an administrative agency created by the Constitution or an initiative statute, has no power:
>
> (a) To declare a statute unenforceable, or refuse to enforce a statute, on the basis of it being unconstitutional unless an appellate court has made a determination that such statute is unconstitutional;
> (b) To declare a statute unconstitutional;

(c) To declare a statute unenforceable, or to refuse to enforce a statute on the basis that federal law or federal regulations prohibit the enforcement of such statute unless an appellate court has made a determination that the enforcement of such statute is prohibited by federal law or federal regulations.

Quite simply, OEHHA could not grant the relief requested in item (e) even if it desired to do so. Lastly in this regard, OEHHA disagrees with petitioner's assertion that Proposition 65 in any way conflicts with the tort principle of "informed consent," which is wholly separate from the implementation of Proposition 65. OEHHA does not know what "other laws" petitioner refers to; however, OEHHA is unaware of any other law that is in conflict with Proposition 65. For all these reasons, the request in item (e) is denied.

(f) Amend Title 22, California Code of Regulations, § 12601(b)(2) to apply the provision regarding prescription drugs also to prescription medical devices.

OEHHA has reviewed petitioner's request at item (f). OEHHA sees no regulatory need to grant the relief sought by amending Title 22, California Code of Regulations, Section 12601(b)(2) as petitioned. OEHHA previously considered and rejected the action sought at the time it promulgated the pertinent regulation. OEHHA is not aware of any changed circumstance since the time of the rulemaking (1989). OEHHA may at some point in the future revisit this issue as part of a more general review of the regulations implementing Proposition 65, but it has no present intention to propose any amendments to Section 12601(b)(2).

(g) Promulgate a regulation exempting intravenous and dialysis therapy prescription medical devices from any Proposition 65 warning requirement.

OEHHA has reviewed item (g) and rejects the request to "promulgate a regulation exempting intravenous and dialysis therapy prescription medical devices from any warning requirement of Proposition 65, in compliance with the legal doctrine of informed consent and other laws of the State of California." First of all, the petition implies that the doctrine of informed consent as a defense to the tort of battery somehow preempts, satisfies, or otherwise "trumps" Proposition 65. That is quite clearly not the case. There is no statutory law or case law to support the notion that Proposition 65 is in conflict with, repugnant to, or otherwise limited by the doctrine of "informed consent." In addition, OEHHA is unaware of any "other laws" with which Proposition 65 is in conflict. Finally in this vein, OEHHA finds the request to be far too broad to be the exercise of good policy, good science, or otherwise lawful to grant the relief sought. A regulation of the type requested is not supported by the weight of the scientific evidence

regarding DEHP, the administration of treatment via intravenous and dialysis therapy prescription medical devices, or otherwise. Accordingly, the request set out at item (g) is denied.

Requested Procedural Actions:

(a) Baxter seeks to have OEHHA "hold a public hearing on the merits of [the] Petition . . ." However, pursuant to Government Code Section 11340.7 no hearing is required in this instance. Section 11340.7 provides in pertinent part as follows:

> Upon receipt of a petition requesting the adoption, amendment, or repeal of a regulation pursuant to Article 5 (commencing with Section 11346), a state agency shall notify the petitioner in writing of the receipt and shall within 30 days deny the petition indicating why the agency has reached its decision on the merits of the petition in writing or schedule the matter for public hearing in accordance with the notice and hearing requirements of that article. (emphasis added).

It is clear that a hearing is required only if the reviewing agency does not respond in writing rejecting the petition on the merits. In effect, the hearing is the start of the regulation adoption process in those situations in which the agency is inclined to grant the petition and initiate a rulemaking. That is not the case here, as is set out above. OEHHA has denied the requested regulatory actions in the petition (OEHHA does at item (d) above point out the proper mechanism for seeking to modify a listing for a chemical). That mechanism is to have the CIC review the chemical. Such a review does not necessitate a public hearing of the sort specified in Government Code Section 11340.7. Rather, the actions of the CIC occur within the context of a public meeting. These meetings are very much like public hearings. The opportunity for public comment is very similar to that provided at a public hearing concerning regulations. The procedures for these meetings are specified in Title 22, California Code of Regulations, Section 12302(d)(1). That provision reads as follows:

> Except as otherwise expressly authorized by statute, all meetings of the Committees, and all subcommittees shall be open to the public and convened only after reasonable public notice of the meeting, including the date, time, location and agenda of items of business to be transacted or discussed, has been provided.

Accordingly, OEHHA rejects the relief sought by this item as unnecessary under both Government Code Section 11340.7 and Title 22, California Code of Regulations, Section 12302(d)(1).

(b) The petition requests "a line of communication between OEHHA and Baxter . . . including but not limited to provision by OEHHA to Baxter two weeks prior to the requested public hearing a list of substantive issues relevant to this petition that OEHHA considers to be in dispute and a list of those scientific and/or factual conclusions that OEHHA recognizes as uncontested."

For the reasons set forth above in item II. (a) immediately above, OEHHA will not be scheduling a hearing pursuant to Government Code Section 11340.7 in this matter. However, OEHHA considers the line of communication with petitioner to be "open."

Should you wish to schedule a meeting to discuss this response to your petition or any other aspect of this matter, please contact Mr. Val Siebal, Chief Deputy Director, at (916) 324-2831.

Sincerely,

Joan E. Denton, Ph.D.
Director

Enclosure

cc: Val F. Siebal
Chief Deputy Director

Carol Rene Brophy, Esq.
McKenna & Cuneo LLP
One Market, Steuart Street Tower
San Francisco, California 94105